Chocolate consumption and risk of stroke

A prospective cohort of men and meta-analysis

Susanna C. Larsson, PhD
Jarmo Virtamo, MD
Alicja Wolk, DMSc

Correspondence & reprint requests to Dr. Larsson: susanna.larsson@ki.se

ABSTRACT

Objective: To investigate the association between chocolate consumption and risk of stroke in men and conduct a meta-analysis to summarize available evidence from prospective studies of chocolate consumption and stroke.

Methods: We prospectively followed 37,103 men in the Cohort of Swedish Men. Chocolate consumption was assessed at baseline using a food-frequency questionnaire. Cases of first stroke were ascertained from the Swedish Hospital Discharge Registry. For the meta-analysis, pertinent studies were identified by searching the PubMed and EMBASE databases through January 13, 2012. Study-specific results were combined using a random-effects model.

Results: During 10.2 years of follow-up, we ascertained 1,995 incident stroke cases, including 1,511 cerebral infarctions, 321 hemorrhagic strokes, and 163 unspecified strokes. High chocolate consumption was associated with a lower risk of stroke. The multivariable relative risk of stroke comparing the highest quartile of chocolate consumption (median 62.9 g/week) with the lowest quartile (median 0 g/week) was 0.83 (95% CI 0.70–0.99). The association did not differ by stroke subtypes. In a meta-analysis of 5 studies, with a total of 4,260 stroke cases, the overall relative risk of stroke for the highest vs lowest category of chocolate consumption was 0.81 (95% CI 0.73–0.90), without heterogeneity among studies ($p = 0.47$).

Conclusion: These findings suggest that moderate chocolate consumption may lower the risk of stroke. *Neurology*® 2012;79:1223–1229

GLOSSARY

BMI = body mass index; **CI** = confidence interval; **ICD-10** = International Classification of Diseases, 10th revision; **LDL** = low-density lipoprotein; **MET** = metabolic equivalent.

Multiple lines of evidence from laboratory experiments and randomized trials indicate that chocolate consumption may be beneficial for cardiovascular health. Flavonoids in chocolate may be protective against cardiovascular disease through antioxidant, antiplatelet, and anti-inflammatory effects.[1] Flavonoids in chocolate may also decrease blood concentrations of low-density lipoprotein (LDL) cholesterol[2] and reduce LDL oxidation[1] as well as improve endothelial function.[1] Furthermore, findings from short-term randomized feeding trials show that chocolate consumption reduces blood pressure,[3,4] which is a strong risk factor for stroke.

The association between chocolate consumption and risk of stroke has been examined in 4 prospective studies.[5–8] Those studies found that chocolate consumption was associated with a lower risk of stroke in women[5,8] or women and men combined,[6,7] but the results were only statistically significant in 2 studies.[7,8] To our knowledge, no study has examined the association between chocolate consumption and risk of stroke in men, and only one study has examined whether the relation varies by stroke subtypes.[8]

From the Division of Nutritional Epidemiology (S.C.L., A.W.), Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; and Department of Chronic Disease Prevention (J.V.), National Institute for Health and Welfare, Helsinki, Finland.

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The aim of this study was to examine the association between chocolate consumption and risk of total stroke and stroke subtypes in a prospective cohort of Swedish men. In addition, we conducted a meta-analysis to summarize available evidence from prospective studies of chocolate consumption and stroke risk.

METHODS

Study population. We used data from the Cohort of Swedish Men. This prospective study began in the autumn of 1997 when all men who were 45 to 79 years of age and resided in 1 of 2 counties of central Sweden (Västmanland and Örebro counties) received a questionnaire that included about 350 items regarding diet and other lifestyle factors. Questionnaires were received from 48,850 men (49% of the source population). These men well represented all Swedish men 45–79 years of age with regard to age distribution, relative body weight, and educational level compared with representative data from the Official Statistics of Sweden.[9]

Standard protocol approvals, registrations, and patient consents. The study was approved by the Ethical Review Board at the Karolinska Institutet (Stockholm, Sweden), and written informed consent was obtained from all men participating in the study.

Baseline data collection. The baseline questionnaire included questions concerning education, weight, height, smoking, physical activity, aspirin use, history of hypertension, family history of myocardial infarction before age 60, alcohol consumption, and diet. We considered participants to have diabetes if they self-reported diabetes on the questionnaire or had a diagnosis of diabetes recorded in the Swedish Hospital Discharge Registry or the Swedish National Diabetes Register. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of height in meters. Pack-years of smoking history were calculated as the number of packs of cigarettes smoked per day multiplied by the number of years of smoking. The questionnaire included questions on activity at work, home/housework, walking/bicycling, and exercise as well as inactivity (watching TV/reading) and hours per day of sleeping and sitting/lying down. The reported time per day spent on different activities was multiplied by the activity's typical energy expenditure requirement expressed in metabolic equivalents (METs). The MET-hours for all activities were then combined to create a MET-hours per day (24-hour) score.[10]

Assessment of chocolate consumption. Chocolate consumption was assessed using a self-administered food-frequency questionnaire that included 96 foods and beverages. Participants were asked to report how often on average they had consumed chocolate and other foods during the past year. For chocolate, participants could choose from 8 prespecified consumption categories, ranging from never to 3 or more times per day. Chocolate consumption in grams was computed by multiplying the frequency of chocolate consumption by 4 age-specific portion sizes (43–54 years, 42 g; 55–63 years, 34 g; 64–71 years, 27 g; 72–77 years, 26 g) obtained from our validation study in Swedish men.[11] In the 1990s, approximately 90% of chocolate consumption in Sweden was milk chocolate, containing approximately 30% cocoa solids.[6]

Case ascertainment and follow-up. Incident cases of first stroke that occurred between January 1, 1998, and December 31, 2008, were identified by linkage of the study population to the Swedish Hospital Discharge Registry, which provides almost complete coverage of the discharges. The International Classification of Diseases, 10th revision (ICD-10), was used to identify stroke events in the cohort. The stroke events were classified as cerebral infarction (ICD-10 code I63), intracerebral hemorrhage (I61), subarachnoid hemorrhage (I60), and unspecified stroke (I64). Information on dates of death was obtained from the Swedish Death Register. The Swedish Hospital Discharge Registry provided information on dates of diagnoses of atrial fibrillation (ICD-10 code I48), which is ascertained with high validity.[12]

Population for analysis. Among the 48,850 men who completed the baseline questionnaire, we excluded those who returned an empty questionnaire (n = 297) and those who had died (n = 55) or had a history of cancer (n = 2,592), cardiovascular disease (n = 5,160), or diabetes (n = 3,243) before the start of follow-up. Furthermore, we excluded men with implausible values for total energy intake (i.e., 3 SDs from the $\log_e$-transformed mean energy intake, n = 400). After these exclusions, 37,103 men remained for the current analyses.

Statistical analysis. Each participant accrued person-time of follow-up from January 1, 1998, until the date of the first stroke event, death, or December 31, 2008, whichever came first. Cox proportional hazard regression models with age as the time scale were used to estimate relative risks (RRs) with 95% confidence intervals (CIs) of stroke by exact quartiles of chocolate consumption based on the distribution in the cohort. Entry time was defined as a subject's age in months at start of follow-up, and exit time was defined as a subject's age in months at stroke diagnosis, death, or end of follow-up. The multivariable model included the following variables: smoking status and pack-years of smoking (never; past <20, 20–39, or ≥40 pack-years; or current <20, 20–39, or ≥40 pack-years), education (less than high school, high school, or university), BMI (<23.0, 23.0–24.9, 25–29.9, or ≥30 kg/m^2), total physical activity (MET-hours/day, quartiles), aspirin use (never, 1–6 tablets/week, or ≥7 tablets/week), history of hypertension (yes or no), diagnosis of atrial fibrillation (yes or no), family history of myocardial infarction before age 60 years (yes or no), total energy intake (kcal/day, continuous variable), coffee consumption (cups/day, quartiles), tea consumption (cups/day, quartiles), and quartiles (g/day) of alcohol, fresh red meat, processed meat, fish, fruits, and vegetables.

Tests for trends across categories were performed by modeling chocolate consumption as a continuous variable in the model using the median value of each category of chocolate. We conducted an analysis stratified by history of hypertension to examine potential effect modification. Tests for interaction were performed with the likelihood ratio test. All statistical analyses were performed with SAS (version 9.1; SAS Institute Inc., Cary, NC). All p values were 2-sided. The study had 80% power ($\alpha = 0.05$) to detect relative risks of <0.84 for total stroke, <0.81 for cerebral infarction, and <0.60 for hemorrhagic stroke, comparing the highest with the lowest quartile of chocolate consumption.

Meta-analysis on chocolate consumption and stroke. We conducted a meta-analysis that included results from the Cohort of Swedish Men (present study) as well as results from previously published prospective studies assessing the association between chocolate consumption and stroke risk. We conducted literature searches on PubMed (http://www.ncbi.nlm.nih.gov/

pubmed) and EMBASE (http://www.embase.com) through January 13, 2012, using the search terms "chocolate" and "stroke." We also searched the reference lists of pertinent articles. No restrictions were imposed.

Study-specific results were combined using a random-effects model.[13] We compared the group with highest chocolate consumption with the group with the lowest consumption. We also conducted a dose-response meta-analysis using the same methods as in previous meta-analyses.[14,15] Statistical heterogeneity among studies was evaluated using I^2 statistics.[16] Small study effects (the tendency for the smaller studies in a meta-analysis to show larger effects) was assessed with a funnel plot[17] and Egger test.[18] We used STATA (StataCorp, College Station, TX) for the statistical analyses.

RESULTS **Cohort of Swedish Men.** During a mean follow-up of 10.2 years (379,094 person-years), we ascertained 1,995 cases of first stroke, including 1,511 cerebral infarctions, 321 hemorrhagic strokes (254 intracerebral hemorrhage, and 67 subarachnoid hemorrhage), and 163 unspecified strokes. Baseline characteristics of the study population by quartiles of chocolate consumption are shown in table 1. Compared with men in the lowest quartile of chocolate consumption, those in the highest quartile were on average younger and were more likely to have a university education and to use aspirin but were less likely to be current smokers and to have a history of hypertension or atrial fibrillation. In addition, men in the highest quartile of chocolate consumption tended to be slightly leaner and had higher consumption of alcohol, red meat, fruits, and vegetables but lower consumption of fish.

High chocolate consumption was associated with a statistically significant lower risk of total stroke in both the age-adjusted and multivariable model (table 2). Compared with men in the lowest quartile of chocolate consumption, those in the highest quartile had a 17% (95% CI 1−30) lower risk of stroke after adjustment for other risk factors for stroke. The results were unchanged after additional adjustment for history of hypercholesterolemia. The age-standardized incidence rates of stroke were 85 per 100,000 person-years among men in the lowest quartile of chocolate consumption and 73 per 100,000 person-years among men in the highest quartile. Blood pressure is a potential intermediate of the relation between chocolate consumption and risk of stroke. The results did not change materially when we removed

Table 1 Baseline characteristics of 37,103 men in the Cohort of Swedish Men by quartiles of chocolate consumption

	Quartile of chocolate consumption				
Characteristic[a]	<12.0 g/wk (0)[b]	12.0–19.5 g/wk (12.5)	19.6–51.5 g/wk (38.4)	≥51.6 g/wk (62.9)	*p* Value[c]
Age, y	61.5	62.9	56.1	54.2	<0.001
Education, university, %	12.9	13.3	20.9	25.6	<0.001
Current smoker, %	28.1	22.6	24.7	24.9	<0.01
Body mass index, kg/m^2	25.9	25.7	25.6	25.3	<0.001
Total physical activity, MET h/d	42.0	41.8	41.6	41.4	<0.001
Aspirin use ≥1 tablet/wk, %	5.2	4.6	4.9	5.5	0.14
Hypertension, %	21.1	21.2	16.1	14.4	<0.001
Atrial fibrillation, %	2.8	2.3	1.7	1.6	0.053
Family history of MI, %	14.2	12.9	15.2	14.9	0.60
Daily dietary intake					
Total energy, kcal	2,466	2,611	2,761	3,036	<0.001
Alcohol, g	9.0	9.8	10.7	11.5	<0.001
Coffee, cups	3.3	3.2	3.4	3.5	0.42
Tea, cups	0.6	0.5	0.6	0.7	0.001
Fresh red meat, g	60.8	60.0	66.7	73.2	<0.001
Processed meat, g	38.7	39.7	41.8	45.0	<0.001
Fish, g	34.3	32.9	29.8	31.0	<0.001
Fruits, g	161	178	189	207	<0.001
Vegetables, g	138	148	146	151	<0.001

Abbreviations: MET = metabolic equivalent of energy expenditure (kcal/kg × g × h); MI = myocardial infarction.
[a] All values are means if not otherwise indicated.
[b] The values in parentheses are the median intake of chocolate.
[c] *p* for trend across quartiles of chocolate consumption was calculated using generalized linear models.

Table 2 Relative risks and 95% confidence intervals of total stroke and stroke subtypes by quartiles of chocolate consumption among 37,103 men in the Cohort of Swedish Men, 1998–2008

	Total stroke				Cerebral infarction			Hemorrhagic stroke		
Chocolate[a]	Person-years	Cases	RR (95% CI)[b]	RR (95% CI)[c]	Cases	RR (95% CI)[b]	RR (95% CI)[c]	Cases	RR (95% CI)[b]	RR (95% CI)[c]
0 g/wk	69,238	504	1.00 (reference)	1.00 (reference)	383	1.00 (reference)	1.00 (reference)	78	1.00 (reference)	1.00 (reference)
12.5 g/wk	113,741	766	0.89 (0.79–0.99)	0.94 (0.84–1.05)	586	0.89 (0.78–1.02)	0.95 (0.83–1.08)	118	0.86 (0.64–1.14)	0.88 (0.66–1.18)
38.4 g/wk	125,489	512	0.89 (0.78–1.00)	0.95 (0.83–1.08)	385	0.89 (0.77–1.03)	0.96 (0.83–1.11)	85	0.84 (0.61–1.15)	0.87 (0.63–1.20)
62.9 g/wk	70,625	213	0.77 (0.65–0.91)	0.83 (0.70–0.99)	157	0.76 (0.63–0.92)	0.83 (0.69–1.01)	40	0.81 (0.55–1.20)	0.84 (0.56–1.25)
p_{trend}			0.006	0.08		0.01	0.14		0.32	0.42

Abbreviations: CI = confidence interval; RR = relative risk.
[a] Median intake of chocolate in each quartile.
[b] Adjusted for age.
[c] Adjusted for age, education, smoking status, and pack-years of smoking, body mass index, total physical activity, aspirin use, history of hypertension, atrial fibrillation, family history of myocardial infarction, and intakes of total energy, alcohol, coffee, tea, fresh red meat, processed meat, fish, fruits, and vegetables.

history of hypertension from the multivariable model (RR 0.82; 95% CI 0.70–0.97). Chocolate consumption was inversely associated with both cerebral infarction and hemorrhagic stroke, but results were not statistically significant in the multivariable model, possibly because of the smaller number of cases and lower statistical power (table 2). In analysis stratified by history of hypertension, an inverse relation between chocolate consumption and risk of total stroke was observed in men without hypertension (RR 0.76; 95% CI 0.62–0.93) but not in men with a history of hypertension (RR 1.04; 95% CI 0.77–1.41) (p for interaction = 0.04).

Meta-analysis. Our literature search identified 4 prospective studies with results on chocolate consumption and stroke risk.[5–8] Among the 5 studies (including the present cohort of men) included in the meta-analysis, 4 were conducted in Europe and 1 in the United States (table 3). Duration of follow-up ranged from about 8 years[6,7] to 16 years.[5] Combined, these studies included a total of 4,260 stroke cases. The overall RR of stroke for the highest vs lowest category of chocolate consumption was 0.81 (95% CI 0.73–0.90), without heterogeneity among studies (figure). One study could not be included in a dose-response meta-analysis.[5] The RR of stroke for a 50 g/week increment of chocolate consumption was 0.86 (95% CI 0.76–0.97), with no heterogeneity among studies (p = 0.21; I^2 = 34.1%). We found evidence of a small study effect in the meta-analysis of the highest vs lowest category of chocolate consumption (Egger test p = 0.03) but not in the dose-response analysis (p = 0.26).

DISCUSSION In this prospective cohort study of men, a high consumption of chocolate was associated with a significant reduced risk of stroke. Men in the highest quartile of chocolate consumption had a 17% lower risk of stroke than those in the lowest quartile. This finding was confirmed in a meta-analysis of 5 prospective studies showing an overall 19% decreased risk of stroke for the highest compared with the lowest category of chocolate consumption. The association between chocolate consumption and stroke risk was similar in men (relative risk = 0.83, present study) and women (relative risks = 0.85 and 0.80, previous studies[5,8]).

Chocolate is a source of flavonoids and is particularly rich in epicatechin, catechin, and procyanidins (polymers of catechins and epicatechins).[19] The flavonoids may reduce the risk of stroke through several biological mechanisms, including antioxidant, antiplatelet, and anti-inflammatory effects as well as by lowering blood pressure, increasing high-density lipoprotein cholesterol, and improving endothelial function. Randomized feeding trials have found that consumption of cocoa beverages[20,21] or dark chocolate[22] produces a reduction in platelet activation and primary platelet aggregation in healthy volunteers. Moreover, randomized trials have shown that intake of high-flavonoid dark chocolate is associated with an improvement in endothelial function, which was indicated by an increase in brachial artery flow-mediated dilation.[23,24] This dilation effect may be mediated through an increase in local production of nitric oxide.[24] Several short-term feeding trials have further shown that consumption of chocolate or cocoa products decreases systolic and diastolic blood pressure[3,4] and may decrease concentrations of LDL cholesterol.[2] In the present study, the association between chocolate consumption and stroke did not change essentially when we removed history of hypertension from the multivariable model. However, this finding does not exclude the possibility that a potential blood pressure–lowering effect of chocolate consumption may explain the observed associa-

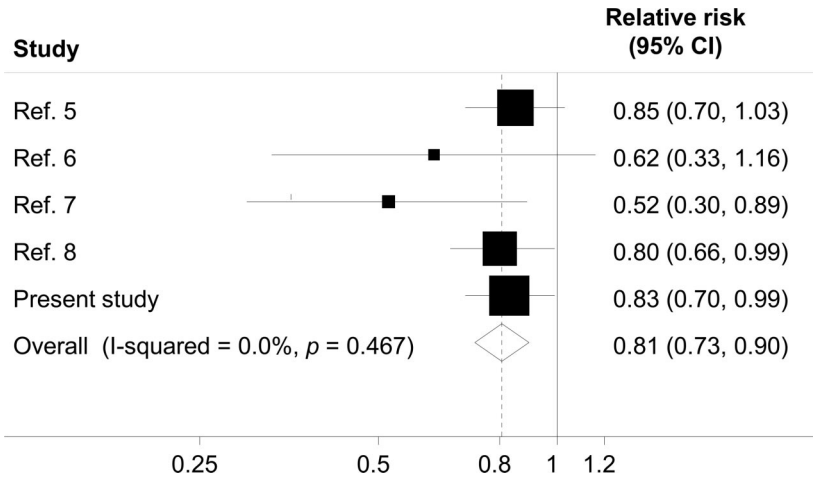
Table 3 Characteristics of prospective studies of chocolate consumption and risk of stroke

Study (reference)	Study name, country	Study population, sex, and age	No. of cases (total cohort)	Chocolate consumption in highest vs lowest category	Adjustments
Mink et al.[5]	Iowa Women's Health Study, United States	Cardiovascular disease–free postmenopausal women, 55–69 yr	469 (34,489)	>0 vs 0 servings/wk	Age, education, BMI, marital status, smoking, blood pressure, waist/hip ratio, physical activity, diabetes, estrogen use, and energy intake
Janszky et al.[6]	Stockholm Heart Epidemiology Program, Sweden	Nondiabetic men and women hospitalized with a myocardial infarction, 45–70 yr	111 (1,169)	Twice or more per week vs never	Age, sex, education, smoking, obesity, physical inactivity, alcohol consumption, filtered coffee consumption, and sweet score
Buijsse et al.[7]	Potsdam arm of the European Prospective Investigation into Cancer, Germany	Cardiovascular disease–free men and women not using antihypertensive medication, 35–65 yr	136 (19,357)	52.5 vs 11.9 g/wk	Age, sex, employment status, education, smoking status, BMI, waist circumference, prevalence of diabetes, occupational physical activity, sports, cycling, and intakes of total energy, alcohol, coffee, tea, red meat, processed meat, dairy, fruits, vegetables, and cereal fiber
Larsson et al.[8]	Swedish Mammography Cohort, Sweden	Cardiovascular disease-free nondiabetic women, 49–83 yr	1,549 (39,227)	66.5 vs 0 g/wk	Age, education, smoking status and pack-years of smoking, BMI, physical activity, aspirin use, history of hypertension, diagnosis of atrial fibrillation, family history of myocardial infarction, and intakes of total energy, alcohol, coffee, tea, red meat, processed meat, fish, fruits, and vegetables
Present study	Cohort of Swedish Men, Sweden	Cardiovascular disease-free nondiabetic men, 45–79 yr	1,995 (37,103)	62.9 vs 0 g/wk	Age, education, smoking status and pack-years of smoking, BMI, physical activity, aspirin use, history of hypertension, diagnosis of atrial fibrillation, family history of myocardial infarction, and intakes of total energy, alcohol, coffee, tea, red meat, processed meat, fish, fruits, and vegetables

Abbreviation: BMI = body mass index.

tion because men with a history of hypertension may have had normal blood pressure at baseline due to treatment for hypertension. This is also consistent with our finding that chocolate consumption was inversely associated with stroke risk among men without a history of hypertension, but not among men with a history of hypertension. Cocoa flavonoids have also been demonstrated to decrease inflammatory markers.[25,26] Of interest, a recent prospective cohort study,[27] followed by an editorial,[28] found that total flavonoid intake was significantly inversely associated with risk of Parkinson disease in men but not in women.

Figure Relative risks of stroke for the highest vs lowest category of chocolate consumption



Squares indicate study-specific relative risks (size of the square reflects the study-specific statistical weight, i.e., the inverse of the variance); horizontal lines indicate 95% confidence intervals (CIs); diamond indicates the summary relative risk with its 95% CI.

The contribution to antioxidant load for different foods and beverages was estimated in a similar cohort of Swedish women. In that study, we observed that chocolate contributed to 4.9% of total antioxidant capacity estimated from the food frequency questionnaire.[29] This value can be compared with the top 5 fruit and vegetable contributors, which were apples/pears (16.1%), oranges (6.2%), potatoes (5.8%), berries (5.0%), and banana (3.5%).[29]

Chocolate also contains caffeine, and consumption of coffee, which is a rich source of caffeine, has been inversely associated with risk of stroke (17% lower risk for 3–4 cups/day of coffee compared with no consumption).[15] The amount of caffeine in chocolate is low (1–15 mg/28 g of milk chocolate) compared with the content in coffee (60–180 mg/150 mL of coffee),[30] and cannot fully explain the observed inverse association between chocolate consumption and stroke risk.

Feeding trials of the effect of chocolate consumption on risk factors for cardiovascular disease have used higher amounts of chocolate than chocolate consumption among men in the highest quintile of chocolate in the present study. However, a random-

ized trial involving 44 adults showed that even a low intake of 6.3 g/day of dark chocolate for 18 weeks significantly reduced blood pressure and improved formation of vasodilative nitric oxide.[31]

The strengths of the present cohort study include a large number of stroke patients and the almost complete follow-up of participants by linkage to population-based Swedish registers. A limitation is that chocolate consumption was self-reported and was only measured at one time point (at baseline). This will inevitably lead to some measurement of chocolate consumption assessment. Any measurement error of chocolate consumption is most likely to be nondifferential, leading to an attenuation of the true association between chocolate consumption and stroke risk. Another limitation is that we could not assess the association between dark chocolate consumption and stroke because information about type of chocolate was not available, and the chocolate consumed in Sweden is mainly milk chocolate, accounting for approximately 90% of chocolate consumption. Men with a high consumption of chocolate tended to be healthier than those with a low chocolate consumption. Although we controlled for major risk factors for stroke, we cannot exclude the possibility that unmeasured or residual confounding may have affected our results. Because this study was population-based and well represented the source population, the results should be generalizable to all men. Results from our meta-analysis further showed that chocolate consumption is inversely associated with risk of stroke in women also.

A meta-analysis inherits the limitations of the studies included. Thus, misclassification of chocolate consumption as well as potential confounding may also have affected our meta-analysis results. The studies included in the present meta-analysis adjusted for major potential confounders. We found evidence of small study effects, with smaller studies showing a stronger inverse association than the larger studies. This small study effect may be due to publication bias. Hence, it is possible that the risk estimate is overestimated.

In summary, results from this prospective study in men and meta-analysis of all available prospective studies of chocolate consumption and stroke suggest that chocolate consumption is inversely associated with risk of stroke. Further studies are required to confirm this finding before any recommendations about chocolate consumption can be given. Because chocolate is high in sugar, saturated fat, and calories, it should be consumed in moderation.

AUTHOR CONTRIBUTIONS

Study concept and design (S.C.L., A.W.), data collection (A.W.), statistical analyses (S.C.L.), manuscript writing (S.C.L.), interpretation of results (S.C.L., J.V., A.W.), and critical revision of manuscript (S.C.L., J.V., A.W.). S.C.L. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DISCLOSURE

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